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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/699,243	10/27/2000	Isabel D.C. Markl	47675-14	5397

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 02/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/699,243	MARKL ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/24/04; 12/6/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,7,8 and 10-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,7,8 and 10-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed September 24, 2004 and December 6, 2004. Currently, claims 1-2, 4, 7-8, 10-15 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 24, 2004 has been entered.

3. Any objections and rejections not reiterated below are hereby withdrawn in view of the amendments to the Claims, applicants' arguments and the 1.132 Declaration filed by Dr. Cathy Lofton-Day.

4. This action contains new grounds of rejection.

New Matter

5. Claims 1-2, 4, 7-8, 10-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "coordinately hypermethylated contiguous CpG island sequences that comprise SEQ ID NO: 36" are included." The amendment

filed February 13, 2004 proposes that the new claim language clarifies that the CpG island must be contiguous, and have additionally required that the CpG island comprise either SEQ ID NO: 36 or 37 and have also requires that the CpG island be coordinately regulated with the comprised sequence. However, the specification does not describe or discuss "coordinately hypermethylated contiguous CpG island sequences that comprise SEQ ID NO: 36". The specification does not appear to contain the words "coordinately hypermethylated." Instead the specification describes CpG island sequences associated with the sequence of the particular SEQ ID NO: is that contiguous sequence of genomic DNA that encompasses at least one nucleotide of the particular SEQ ID NO: sequence. This description does not support coordinately hypermethylated contiguous CpG island sequences that comprise SEQ ID NO: 36. The specification fails to describe or discuss what "coordinately hypermethylated" encompasses or requires. Coordinately hypermethylated has not been defined in the instant specification. The concept of "coordinately hypermethylated contiguous CpG island sequences that comprise SEQ ID NO: 36" does not appear to be part of the originally filed invention. Therefore, "coordinately hypermethylated contiguous CpG island sequences that comprise SEQ ID NO: 36" constitutes new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-2, 4, 7-8, 13-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to "coordinately hypermethylated contiguous CpG island sequence that comprise SEQ ID NO: 36 or 37. The claims are also drawn to a kit and DNA sequences selected a probe or primer comprising at least 12 contiguous nucleotides of SEQ ID NO: 34-37.

The specification describes sequencing 103 "novel" sequences. The specification fails to teach the chromosomal location, the gene, or the cDNA of these DNA sequence fragments. The specification fails to describe contiguous CpG islands of SEQ ID NO: 34-37.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to

disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of specifies have been described by their complete structure. In the instant case, Applicant has defined only a fragment of a nucleic acid sequence. Applicant has not disclosed any genomic DNA sequences and particularly has not disclosed any intron sequences or regulatory sequences. Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

The claims encompass "coordinately hypermethylated contiguous CpG island sequences that comprise SEQ ID NO: 36 or 37." For illustration purposes, the following embodiment is encompassed within the scope of the claims but fails to be described.

**********(SEQ ID NO 36) ******** (CpG) *********.

Here, this CpG region is encompasses within the same larger CpG island as SEQ ID NO: 36 and is contiguous with SEQ ID NO: 36. However, the flanking or context sequence of "CpG" has not been disclosed or described. No precise definition, such as by structure, formula, chemical name, or physical properties has been provided.

The specification appears to merely provide a wish or plan for obtaining the claimed chemical invention which does not constitute description of the subject matter.

Similar to Example 7 of the Written Description guidelines, the specification teaches a fragment of a cDNA or genomic DNA, but does not provide the full cDNA or genomic DNA.

With respect to Claims 7-8, the claimed sequences have not been adequately described. The claims are drawn to a probe or primer comprising at least 12 contiguous nucleotides from SEQ ID NO: 34-38. The genus of nucleic acids encompassed by the claims is very large. This nucleic acid broadly encompasses a nucleic acid with no length limitation which minimally comprises 12 nucleotides in common with SEQ ID NO: 34-38. Moreover, where the probe comprises at least 12 nucleotides from SEQ ID NO: 34-38 the nucleic acid broadly reads on the gene from the CpG island was extracted, which has not been described. Variants, including polymorphisms, mutations, splice variants, for example. The full length DNA comprising SEQ ID NO: 34-38 has not been described, thus full length genes comprising a smaller portion has not been described.

Response to Arguments

The response traverses the rejection. The response asserts that the claims have been amended. The newly amended claims have been considered and discussed above.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-2, 4, 7-8, 10-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to a method of diagnosis or prognosis of breast cancer using SEQ ID NO: 36 or coordinately hypermethyalted continguous CpG island sequences that comprise SEQ ID NO: 36 by performing a methlyation assay to determine a diagnosis; a method of diagnosis or prognosis of prostate, breast or colon cancer using SEQ ID NO: 37 or coordinately hypermethyalted continguous CpG island sequences that comprise SEQ ID NO: 37 by performing a methlyation assay to determine a diagnosis. The claims also encompass nucleic acids consisting of SEQ ID NO: 34, 35, 38.

The specification clearly states that "unfortunately, the mere knowledge of the basic existence of altered methylation of CpG dinucleotides within CpG islands of cancer cells relative to normal cells, or of the fact that in particular instances such methylation changes result in altered gene expression (or chromatin structure or stability), is inadequate to allow for effective diagnostic, prognostic and therapeutic application of this knowledge" (page 2, lines 31-35). The specification continues to state "this is because only a limited number of CpG islands have been characterized, and thus there is insufficient knowledge, as to which particular CpG islands, among many, are actually involved in, or show significant correlation with cancer or the etiology

thereof. Moreover, complex methylation patterns, involving a plurality of methylation-altered DNA sequences, including those that may have the sequence compositions to qualify as CpG islands, may exist in particular cancers" (page 3, lines 1-5). Therefore, there is a need in the art to identify and characterize specific methylation altered DNA sequences, and to correlate them with cancer to allow for their diagnostic, prognostic and therapeutic application (page 3, lines 7-10). The specification teaches the invention provides for 103 DNA sequences having distinct methylation patterns in cancer, as compared to normal tissue (page 5, lines 35-36). These "methylation-altered DNA sequence embodiments correspond to 103 DNA fragments isolated from bladder and prostate cancer patients" (page 6, lines 1-2). Genomic DNA was isolated from tissue of bladder or prostate cancer patients and identified as either hypermethylated or hypomethylated (page 6).

The art clearly illustrates that certain genes, including GSTP1, HIC-1, and p16, are hypermethylated and this is indicative of certain cancers (US Pat. 5,552,277; 5,846,712; 5,856,094).

Neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed. First, with respect to SEQ ID NO: 34, 35, and 38, the specification clearly teaches that "unfortunately, the mere knowledge of the basic existence of altered methylation of CpG dinucleotides within CpG islands of cancer cells relative to normal cells, or of the fact that in particular instances such methylation changes result in altered gene expression (or chromatin structure or stability), is inadequate to allow for effective diagnostic, prognostic and therapeutic application of

this knowledge" (page 2, lines 31-35). The instant specification does not appear to have performed any more experimentation than the mere determination that a basic existence of altered methylation of CpG dinucleotides within CpG islands of cancer cells relative to normal. Therefore, the specification appears to be indicating that this is inadequate to allow for effective diagnostic, prognostic or therapeutic application of this knowledge. In essence, it appears as though the specification teaches that the instant invention is not enabled for use in diagnostic, prognostic or therapeutic applications. In order to use this information, the skilled artisan would be required to sample a population of individuals and assess whether each SEQ ID NO: 34, 35, 38 is associated or differentially expressed in cancer. This experimentation would be trial and error experimentation which would not have predictable results for the reasons provided in the specification, namely "this is because only a limited number of CpG islands have been characterized, and thus there is insufficient knowledge, as to which particular CpG islands, among many, are actually involved in, or show significant correlation with cancer or the etiology thereof. Moreover, complex methylation patterns, involving a plurality of methylation-altered DNA sequences, including those that may have the sequence compositions to qualify as CpG islands, may exist in particular cancers" (page 3, lines 1-5). In the event that detection of cancer, is not enabled, it is unclear how the polynucleotides of SEQ ID NO: 34, 35, and 38 may be used without further undue and unpredictable experimentation. To use these polynucleotides as probes to determine whether they are associated with cancer methylation would constitute research which would require further undue and unpredictable experimentation. As is clear from the

prior art and the instant application, each nucleic acid is not predictably associated with any particular cancer. The indication that one prostate cancer sample indicated a hypermethylation of the region is not indicative that any and all cancers have the same methylation regions. For example, the bladder cancer samples exemplified in the specification do not appear to have hypermethylation of SEQ ID NO: 34, 35, 38. Therefore, it is unpredictable whether hypermethylation of SEQ ID NO: 34, 35, 38 is a general marker for all cancers, or whether there is a smaller class of cancers which SEQ ID NO: 34, 35, 38 are markers, or finally whether the sequence may only be expressed in prostate cancer. Therefore, while one could conduct additional experimentation to determine whether, e.g, SEQ ID NO: 34, 35, and 38 might be hypermethylated in e.g., certain types of cancers, the outcome of such research cannot be predicted and such further research and experimentation are both unpredictable and undue.

Additionally, the specification has not taught that a predictable correlation exists between nucleic acids which are "coordinately methylated contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ ID NO: 36-37". The specification has not described any "coordinately methylated contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ ID NO: 36-37", therefore, it is unpredictable that "coordinately methylated contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ ID NO: 36-37" are indicative of cancers absent unpredictable and undue experimentation. The skilled artisan would first be required to

determine "coordinately methylated contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ ID NO: 36-37" and then assay these unknown sequences to determine whether or not they are hypermethylated or hypomethylated and then whether this aberrant methylation status is associated with cancer. Moreover, the art does not support the idea that all contiguous CpG islands are associated with cancer of prostate, colon or breast. For example, in CACNA1G (see Toyota et al. Cancer Research, Vol. 59, pages 4535-4541, September 1999), a detailed analysis was provided for CpG islands within the gene. The eight regions each behaved very differently. For example Regions 1 and 2 behaved in a concordant manner. Region 3 had either no methylation or very low levels of methylation. Regions 5, 6, 7 behaved differently than regions 1-3. Regions 4, 8 behaved differentially again. Thus, with regards to hypermethylation in cancer, the CpG region upstream of CACNA1G appears to be behave independently (page 4538, col. 1). Therefore, since the art provides examples where CpG islands act in predictable ways (cited by applicant) and examples where CpG islands act independently (cited by examiner, namely Toyota, for example), it is unpredictable whether the instant CpG islands act in a predictable or independent manner. Therefore, it is unpredictable that regions coordinately hypermethylated contiguous with SEQ ID NO: 36-37 are associated with cancer.

Therefore, based upon the unpredictability and the undue experimentation which would be required to be performed prior to practicing the full scope of the method, the instant specification has not enabled the instant claims.

Response to Arguments

The response traverses the rejection. The response asserts that the claims have been adequately enabled. In responding to the examiner's rejection, applicants have set forth several reasons for traversal which will be addressed in the order argued.

The affidavit under 37 CFR 1.132 filed May 23, 2003 is insufficient to overcome the rejection of claims 1-2, 4, 7-12 based upon enablement as set forth in the last Office action. The declaration filed by Dr. Cathy Lofton-Day of May 23, 2003 has been thoroughly reviewed, but found not persuasive to enable the full scope of the instant claims.

The declaration is drawn to SEQ ID NO: 36 and 37. The claims encompass "coordinately hypermethylated" and SEQ ID NO: 34, 35, 38, for example. Based upon the unpredictability discussed above, there is no evidence of record to suggest that coordinately hypermethylated contiguous CpG island sequences that comprise SEQ ID NO: 36 are associated with breast cancer. Neither the specification, the declaration or the art provide any evidence of a correlation between coordinately hypermethylated contiguous CpG island sequences that comprise SEQ ID NO: 36 with breast cancer.

Moreover, the data is silent with respect to CpG islands which are "coordinately hypermethylated contiguous CpG island sequences that comprise SEQ ID NO: 36." contiguous with or encompassing at least one nucleotide of SEQ ID NO: 35-38. It is noted that MPEP 2164.05(a), "a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention." The instant showing is not commensurate in scope with the claims,

as there is no evidence that coordinately hypermethylated contiguous CpG island sequences that comprise SEQ ID NO: 36 are associated with breast cancer, for example.

Finally, the response traverses the rejection with respect to the "coordinately hypermethylated contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ ID NO: 36-37" within the scope of the claims. The specification teaches that the CpG island sequence associated with the sequence of a particular SEQ ID NO: is that contiguous sequence of genomic DNA that encompasses at least one nucleotide of the particular SEQ ID NO: sequence and satisfies the criteria of having both a frequency of CpG diunucleotides corresponding to an Observed/Expected Ration >0.6, and a GC content >0.5 (page 3, lines 24-28). This argument has been reviewed but is not convincing because the specification has not provided a representative number of associated sequences that comprise SEQ ID NO: 36-37. The specification has not provided a larger portion of a CpG island. Therefore, detecting an associated sequence has not been taught in the specification. Moreover, the art does not support the idea that coordinately hypermethylated contiguous CpG island sequences that comprise SEQ ID NO: 36 are associated with cancer of prostate, colon or breast. For example, in CACNA1G (see Toyota et al. Cancer Research, Vol. 59, pages 4535-4541, September 1999), a detailed analysis was provided for CpG islands within the gene. The eight regions each behaved very differently. For example Regions 1 and 2 behaved in a concordant manner. Region 3 had either no methylation or very low levels of methylation. Regions 5, 6, 7 behaved differently than regions 1-3.

Regions 4, 8 behaved differentially again. Thus, with regards to hypermethylation in cancer, the CpG region upstream of CACNA1G appears to be behave independently (page 4538, col. 1). Therefore, since the art provides examples where CpG islands act in predictable ways (cited by applicant) and examples where CpG islands act independently (cited by examiner, namely Toyota, for example), it is unpredictable whether the instant CpG islands act in a predictable or independent manner. Finally, the declaration filed is not commensurate in scope with the instant claims. The declaration filed is directed to SEQ ID NO: 36 and 37. There is no showing of any additional sequences. It is noted that MPEP 2164.05(a), "a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention." Therefore, it is unpredictable that regions contiguous with SEQ ID NO: 36-37 are associated with cancer. The response asserts that the claims have been amended to encompass "only those contiguous CpG island that would also correlate with the same respective cancer(s)." This argument has been thoroughly considered and not found persuasive because to determine which sequences are "coordinately hypermethylated contiguous CpG island sequences that comprise SE QID NO:36" would require unpredictable and undue experimentation. As discussed at length above, CACNA1G is a very specific example of contiguous regions within the same CpG island which do not share hypermethylation. To determine which regions are and which regions are not associated with cancer requires further undue and unpredictable experimentation. The specification does not provide any guidance in

determining which sequences are "coordinately hypermethlyated" without performing the further unpredictable and undue experimentation.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-2, 4, 7-8, 10-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-2, 4, 7-8, 10-15 are indefinite over the recitation "coordinately hypermethylated." The specification does not appear to define the recitation "coordinately hypermethylated." Coordinately is defined as in a coordinated manner www.cogsci.princeton.edu/cgi-bin/webwn. It is unclear how this definition is related to hypermethylated. It is unclear whether coordinately hypermethylated refers to the amount of methylation. It is unclear how many CG's need to be hypermethylated to be considered coordinately hypermethylated contiguous CpG island sequence. It is unclear whether coordinately hypermethylated refers to the location of the hypermethylated CpG sequences. Thus, the metes and bounds of the claimed invention are unclear.

Conclusion

9. No claims allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

Jeanine Goldberg

Jeanine Goldberg
Primary Examiner
February 7, 2005